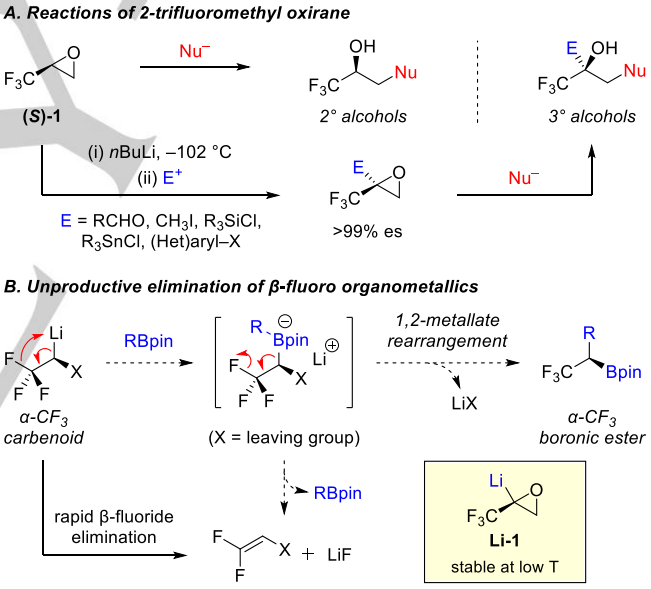
Ring-Opening Lithiation–Borylation of 2-Trifluoromethyl Oxirane: A Route to Versatile Tertiary Trifluoromethyl Boronic Esters

Meganathan Nandakumar, Belén Rubial, Adam Noble, Eddie L. Myers,* and Varinder K. Aggarwal*

Abstract: Stereogenic trifluoromethyl-substituted carbon centres are highly sought-after moieties in pharmaceutical and agrochemical discovery. Here, we show that lithiation–borylation reactions of 2-trifluoromethyl oxirane give densely functionalised and highly versatile trifluoromethyl-substituted α-tertiary boronic esters. The intermediate boronate complexes undergo the desired 1,2-rearrangement of the carbon-based group with complete retentive stereospecificity, a process that was only observed in non-polar solvents in the presence of TESOTf. Although the trifluoromethyl group adversely affects subsequent transformations of the α-boryl group, Zweifel olefinations provide trifluoromethyl-bearing quaternary stereocenters substituted with alkenes, alkynes and ketones.

Organofluorine compounds continue to find broad application, particularly in medicinal chemistry where the replacement of a C–H or C–OH bond with a C–F bond often provides more potent lead molecules with desirable metabolic profiles.[1] In 2018 alone, 17 of the 59 new drugs contained fluorine.[2] This structural change is also a rewarding strategy in catalyst design,[3] radiodiagnostics[4] and materials research,[5] thus fueling interest in the development of methods for transforming easily accessible functional groups into either a fluorine atom or a fluorine-containing group (e.g. CF_3).[6] 2-Trifluoromethyl oxirane (**1**), which is readily accessible on scale in either enantiomer through Jacobsen's kinetic resolution,[7] is an important chiral pool starting material for the synthesis of trifluoromethyl-containing organic molecules (Scheme 1A). In the presence of nucleophiles, it undergoes ring-opening at the less-sterically hindered methylene position to give α-trifluoromethyl secondary alcohols.[8] Stereospecific metalation of the more acidic methine followed by electrophile trapping or cross-coupling and subsequent epoxide-opening leads to α-trifluoromethyl tertiary alcohols.[9]

α-Trifluoromethyl boronic esters are potentially valuable intermediates for the preparation of diverse trifluoromethylated products due to the versatility of the boronic ester,[10,11] which can be stereospecifically transformed into a variety of functional groups.[12] However, there are only a limited number of methods for their preparation. For example, they have been prepared through the reaction of 2,2,2-trifluorodiazoethane with organoboron compounds.[10a,b] Asymmetric versions of this reaction have also been developed using engineered enzymes.[11] Dilman showed that trifluoromethyl boronate complexes derived from the reaction of α-bromo boronic esters with CF_3SiMe_3/KF only undergo the desired 1,2-metallate rearrangement under forcing conditions, thus highlighting the reduced nucleophilicity of the trifluoromethyl group.[10c] Unfortunately, it is difficult to render such methodology asymmetric without the use of enzymes. We postulated that enantiopure α-trifluoromethyl boronic esters could be accessed via lithiation–borylations of trifluoromethyl-substituted carbenoids (Scheme 1B). The main challenge with this approach was the stability of the organolithium and organoboronate intermediates. Specifically, when a fluorine atom is α or β to a metal atom, unproductive elimination usually dominates.[13] However, we anticipated that the use of lithiated trifluoromethyl oxirane **Li-1** (Scheme 1B) would mitigate the propensity to undergo fragmentation because (i) **Li-1** is configurationally stable at ultra-low temperatures;[9,13g] and (ii) boronate complexes derived from lithiated epoxides can be activated to undergo 1,2-metallate rearrangement at low temperatures through the addition of Lewis acids.[14] Herein, we report our successful development of lithiation–borylation reactions of **1** for the synthesis of α-trifluoromethyl-substituted tertiary boronic esters (Scheme 1C), and detail how the trifluoromethyl group led to a number of surprises related to the 1,2-metallate rearrangement.



Scheme 1. Reactions of 2-trifluoromethyl oxirane and trifluoromethyl-substituted carbenoids.

We began our studies by establishing conditions for formation of the boronate complexes from **Li-1**. Owing to the configurational instability of **Li-1**, it was generated by deprotonation of **1** with a hindered base (LDA) at ultra-low temperatures (−102 °C) in the presence of the boronic ester (2-phenethyl boronic ester, **2a**) so that it would be immediately trapped as the boronate.[14] ^{11}B NMR analysis of the reaction

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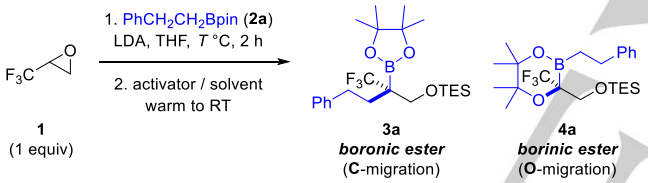
mixture showed complete boronate complex formation (Table 1, entry 1). However, the boronate did not undergo the desired 1,2-metalate rearrangement upon warming to room temperature; instead, slow fragmentation returned the starting boronic ester. To promote 1,2-metalate rearrangement, Lewis acids were added to the freshly prepared boronate complex at low temperature, followed by warming to room temperature. While the $MgBr_2$ and BF_3 did not promote 1,2-metallate rearrangement to any extent (entries 2 and 3), TESOTf promoted the rearrangement in quantitative yield (entry 4). Analysis of the mixture revealed an 8:92 mixture of the desired boronic ester **3a** and borinic ester **4a**, the latter originating from 1,2-migration of one of the pinacol oxygen atoms (O-migration). The unusually strong preference for contra-thermodynamic O-migration over C-migration[15] provided one of many surprises at how the CF_3 group profoundly changes reactivity in this project. As the reactivity of boronates can be strongly dependent on solvent,[16] we performed a THF→toluene solvent exchange after formation of the boronate, with subsequent addition of TESOTf at −102 °C. Upon warming to room temperature, ^{1}H NMR analysis showed a 70:30 mixture of **3a**/**4a** formed in 80% yield *now in favour of the C-migration* product (entry 5). Lithiation with in situ trapping as the boronate could also be conducted more conveniently at −78 °C, giving an improved 80:20 mixture of **3a**/**4a** and allowing isolation of **3a** in 71% yield (entry 6).

Table 1. Optimization of reaction conditions.[a]



1 (1 equiv) — **3a** ***boronic ester*** (**C**-migration) — **4a** ***borinic ester*** (**O**-migration)

Entry	*T*	Activator/Solvent	Yield[b] (**3a**+**4a**)	**3a**/**4a**[b]
1	−102 °C	-	0%	-
2	−102 °C	$MgBr_2.OEt_2$/THF	0%	-
3	−102 °C	$BF_3.OEt_2$ /THF	0%	-
4	−102 °C	TESOTf/THF	100%	8:92
5	−102 °C	TESOTf/toluene	80%	70:30
6	−78 °C	TESOTf/toluene	92% (71%)[c]	80:20

[a] Addition of LDA (1.3 equiv) to **1** (0.22 mmol) and **2** (1.25 equiv) in THF (1 mL). [b] Determined by ^{19}F NMR analysis using 2,4-dichloro-1-(trifluoromethyl)benzene as internal standard. [c] Yield of isolated **3a**.

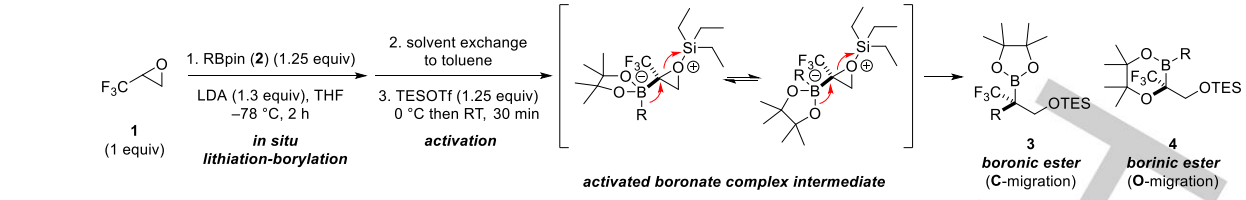
We investigated the scope of this transformation with respect to the boronic ester. Primary aliphatic boronic esters bearing a range of functional groups, including aryl (**2a**), alkyl (**2b**), heteroaryl (**2c**), azidyl (**2d**), silylether (**2e**), alkenyl (**2f**), allyl (**2g**) and benzyl (**2h**) were transformed to give 70:30–91:9 mixtures in favour of the C-migration product (Scheme 2A). Notably, the boronate complex bearing a methyl group, which is normally a poor migrating group,[17] underwent 1,2-metalate rearrangement to give C-migration product **3i** exclusively.

Transformation of secondary boronic esters gave more variable levels of selectivity (Scheme 2A). For example, cyclopropyl boronic ester (**2j**) afforded a 73:27 mixture of **3j**/**4j**, whereas cyclobutyl boronic ester (**2k**) afforded the C-migration product exclusively. Although, cyclopentyl (**2l**) and cyclohexyl (**2m**) boronic esters were transformed with poor levels of selectivity (~1:1), switching to the even less polar solvent, pentane, allowed a return to serviceable levels of selectivity in favour of the C-migration product: 75:25 and 90:10 for **3l**/**4l** and **3m**/**4m**, respectively. A general trend was clear: the smaller the organic group on the boron moiety, the higher the level of selectivity in favour of the C-migration product.

Investigation of aromatic substrates (**3n–3s**) revealed that electron-donating ring substituents promoted C-migration. For example, the *p*-CN aryl boronic ester (**2n**) gave a 48:52 mixture of **3n**/**4n**, while the *p*-MeO substrate (**2s**) gave a 86:14 mixture of **3s**/**4s**. More electron-rich heteroaromatic boronic esters, (**2t–2v**) gave excellent selectivity for the C-migration product. Notably, a boronic ester bearing an *ortho* substituent (*o*-tolyl, **3r)** also gave high levels of C-migration. Alkenyl boronic esters (**2w** and **2x**) were transformed into the corresponding C-migration product in moderate yield but with high levels of selectivity for C-migration.

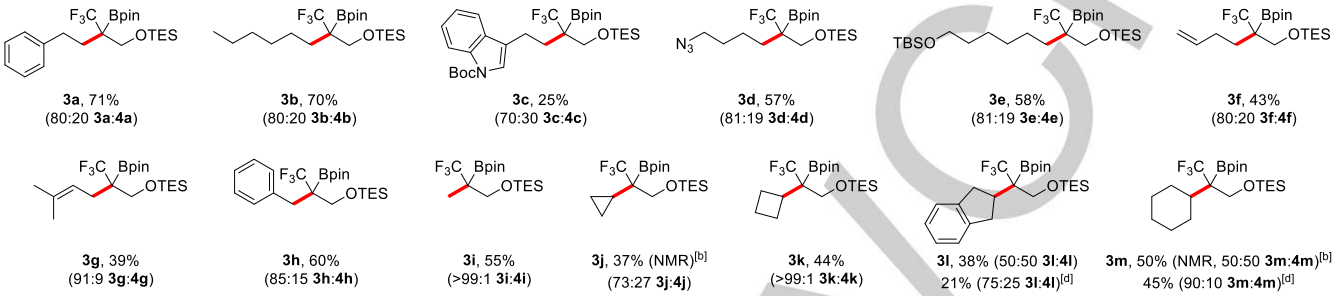
By using (*1S*)-trifluoromethyl oxirane (**(*S*)-1**), which was prepared in high enantiomeric excess (>99.9% ee) through Jacobsen's kinetic resolution,[7] a range of primary alkyl, aryl and heteroaryl boronic esters were transformed into the desired C-migration products with excellent stereospecificity (98:2–99.9:0.1 er, Scheme 2C). Slightly lower levels of stereospecificity was observed with a secondary alkyl boronic ester (94:6, Scheme 2C). Diastereospecific reactions of enantiopure chiral boronic esters gave the corresponding products in excellent diastereospecificity (Scheme 2D). Notably, enantiomeric secondary benzylic boronic esters **(*S*)-2z** and **(*R*)-2z** provided diastereomeric products with no matched/mis-matched effects. Interestingly, although **(*S*)-2z** was transformed into the C-migration product exclusively, **(*R*)-2z** gave the C-migration product with moderate levels of selectivity (66:34).

Finally, we explored the synthetic utility of the tertiary boronic ester products through stereospecific transformations of the C–B bond (Scheme 3). Oxidation of **7a** using basic hydrogen peroxide with concomitant deprotection of the TES group afforded tertiary–primary 1,2-diol **(*S*)-7a** in good yield and with perfect levels of stereospecificity (Scheme 3A). Unfortunately, all attempted one-carbon homologations of **3a** using Matteson's conditions ($LiCH_2I$ or $LiCH_2Cl$, –78 °C to RT) resulted in exclusive β-elimination of fluoride to give 1,1-difluoroalkene **6** (Scheme 3B).[15b] This mirrors a previously reported Matteson homologation of a less-hindered secondary boronic ester bearing an α-CF_3 group, which provided a mixture of homologation and elimination products.[10b] Despite this result, we were optimistic that the tertiary boronic esters could be transformed through a Zweifel olefination, owing to the superior leaving group ability of the intermediate iodonium species.[18] Under standard Zweifel conditions (vinyl lithium, –78 °C; I_2, MeOH, –78 °C; NaOMe, MeOH, –78 °C to RT),[15b,19] elimination to difluoroalkene **6** occurred; however, lowering the temperature to –100 °C prevented elimination and provided alkene **(*S*)-7b** in 79% yield with perfect enantiospecificity. Notably, Zweifel-type olefinations involving more hindered alkenyllithiums were successful through generation of the boronate at –78°C. For example, reaction with lithiated enol carbamate followed by elimination with LDA gave alkyne **(*S*)-7c** in 69% yield,

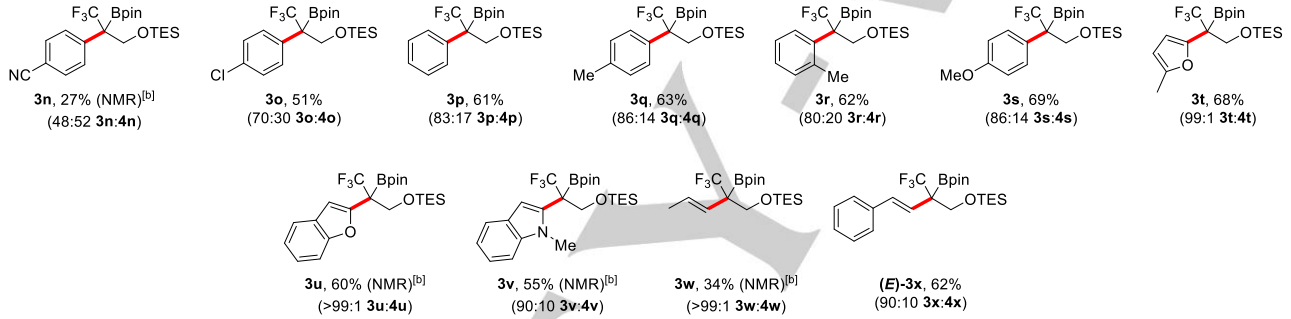


Scope of sp³- and sp²-hybridized boronic esters[a]

A) Scope of aliphatic boronic esters

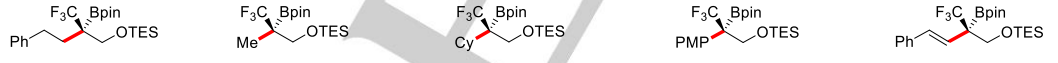


B) Scope of aromatic and vinylic boronic esters

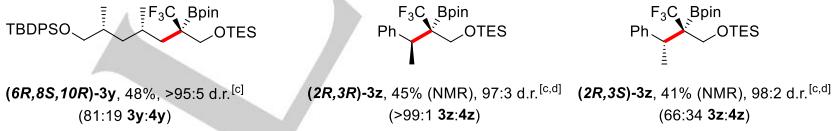


Stereospecific synthesis of α-trifluoromethyl substituted tertiary boronic esters [a]

C) Enantiospecific synthesis of α-trifluoromethylated tertiary boronic esters[e]



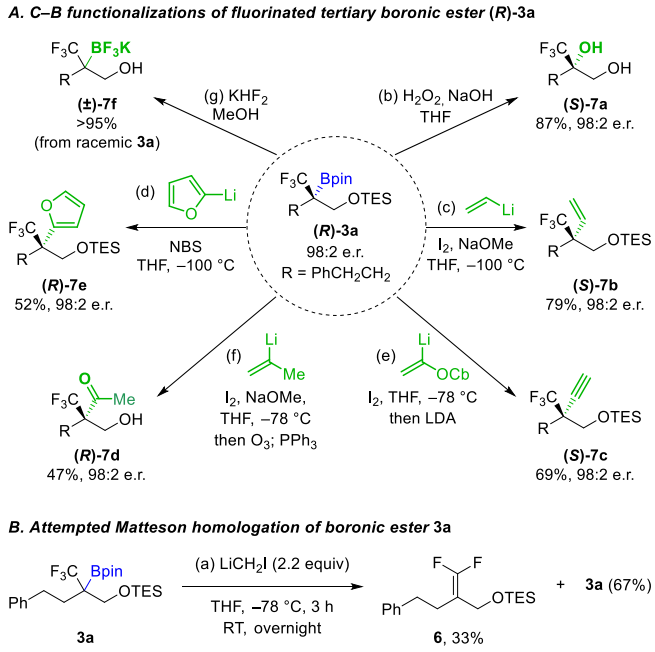
D) Diastereospecific synthesis of α-trifluoromethylated tertiary boronic esters



Scheme 2. Scope of lithiation-borylation of 2-trifluoromethyl oxirane. [a] Yields refer to isolated C-migration product unless otherwise indicated. C:O ratios were determined by ^{19}F NMR analysis of the crude reaction mixture [b] NMR yields determined by ^{19}F NMR analysis of crude reaction mixture. [c] d.r. determined by ^{19}F NMR analysis of isolated compounds. [d] Solvent exchange to pentane. [e] e.r. determined by HPLC analysis of isolated compounds.

and with perfect levels of enantiospecificity.[20] Furthermore, the use of 2-propenyllithium followed by ozonolysis gave methyl ketone **(*R*)-7d** in 47% yield.[19,21] NBS-mediated coupling with 2-furyllithium gave arylated product **(*R*)-7e** in moderate yield.[22] Finally, potassium trifluoroborate salt **7f** could be prepared in excellent yield by treating **3a** with KHF_2 in MeOH.[23]

In conclusion, tertiary α-trifluoromethyl substituted boronic esters can be generated through stereospecific lithiation–borylation of 2-trifluoromethyl oxirane. The success of this protocol is attributed to the use of Lewis acid activation to promote ring-opening 1,2-metalate rearrangement at low temperatures, thus avoiding unproductive elimination of fluoride. Interestingly, the presence of the trifluoromethyl group seems to promote undesired migration of one of the oxygen ligands on boron (O-migration), which competes with the desired C-migration, but can be minimized through the use of non-polar solvents. The boronic ester group of the products can be transformed into a hydroxy group or a variety of carbon-based functional groups (aryl, alkenyl, alkynyl, actl) through Zwiefel-type olefination reactions, thus providing a diverse selection of compounds containing a trifluoromethyl-bearing quaternary centre.



Scheme 3. Stereospecific C–B functionalizations of boronic ester (*R*)-**3a**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: fluorine• trifluoromethyl • stereospecific • quaternary center • lithiation-borylation

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Layout 2:

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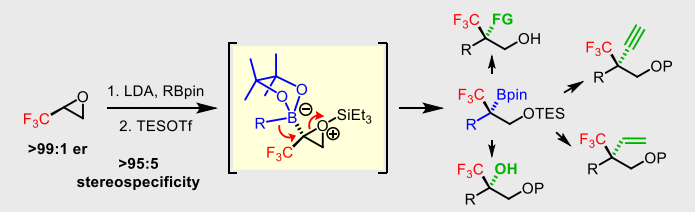

Lithiation-borylation of 2,3-epoxy-1,1,1-trifluoropropane has been developed for the stereospecific synthesis of enantioenriched tertiary α-trifluoromethylated boronic esters and their stereospecific conversion to a variety of fluorinated molecules bearing a chiral quaternary center is described.

*M. Nandakumar, B. Rubial, A. Noble, E. L. Myers, V. K. Aggarwal**

Page No. – Page No.

Ring-Opening Lithiation–Borylation of 2-Trifluoromethyl Oxirane: A Route to Versatile Tertiary Trifluoromethyl Boronic Esters